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Commentary

Smoking Is Associated With COVID-19 Progression: A Meta-analysis

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Abstract

Introduction: Smoking depresses pulmonary immune function and is a risk factor contracting other infectious diseases and more serious outcomes among people who become infected. This paper presents a meta-analysis of the association between smoking and progression of the infectious disease COVID-19.

Methods: PubMed was searched on April 28, 2020, with search terms “smoking”, “smoker*”, “characteristics”, “risk factors”, “outcomes”, and “COVID-19”, “COVID”, “coronavirus”, “sar cov-2”, “sar cov 2”. Studies reporting smoking behavior of COVID-19 patients and progression of disease were selected for the final analysis. The study outcome was progression of COVID-19 among people who already had the disease. A random effects meta-analysis was applied.

Results: We identified 19 peer-reviewed papers with a total of 11,590 COVID-19 patients, 2,133 (18.4%) with severe disease and 731 (6.3%) with a history of smoking. A total of 218 patients with a history of smoking (29.8%) experienced disease progression, compared with 17.6% of non-smoking patients. The meta-analysis showed a significant association between smoking and progression of COVID-19 (OR 1.91, 95% confidence interval [CI] 1.42-2.59, $p = 0.001$). Limitations in the 19 papers suggest that the actual risk of smoking may be higher.

Conclusions: Smoking is a risk factor for progression of COVID-19, with smokers having higher odds of COVID-19 progression than never smokers.

Implications: Physicians and public health professionals should collect data on smoking as part of clinical management and add smoking cessation to the list of practices to blunt the COVID-19 pandemic.

Introduction

COVID-19, the coronavirus-transmitted infectious disease, has caused a worldwide pandemic. Smoking^{1,2} and e-cigarette use³ increase risk and severity of pulmonary infections because of damage to upper airways and a decrease in pulmonary immune function. In particular, smokers have a higher risk of infection and mortality from Cov-MERS.⁴ Two reviews^{5,6} of the first five papers presenting data on smoking and COVID-19 reached different conclusions. Another review described six published case series presenting data on smoking among COVID-19 patients but did not draw a conclusion about the

association of severity of COVID-19 with smoking.⁷ We reviewed and summarized 19 peer-reviewed papers presenting data on the association between smoking and severity of COVID-19.

Methods

We conducted a systematic search using PubMed on April 28, 2020, with the search term: ((smoking) OR (characteristics) OR (risk factors) OR (outcomes) OR (smoker*)) AND ((COVID-19) OR (COVID) OR (coronavirus) OR (sars cov-2) OR (sars cov 2)) for studies published between January 1, 2020 and April 28, 2020. One

author extracted information for each study, screened the abstract or the full text, with questions resolved through discussion among both authors. There were no language restrictions. A total of 907 studies were retrieved through the search, of which 19,⁸⁻²⁶ 16 from China, 1 from Korea, and 2 from the United States, included data on smoking behavior and COVID-19 disease progression (Supplementary Table S1). Seventeen studies^{9-12,14-26} were based on hospitalized patients and two^{8,13} included both hospitalized patients and outpatients.

The exposure group for our analysis were those who had a history of smoking (current smokers or former smokers) and unexposed group was never smokers. Nine studies^{10,12,14,18,20,21,23,25,26} assessed whether the patient was a “current smoker,” five studies^{8,9,13,16,24} assessed whether the patient was a current or former smoker (as separate categories), and five studies^{11,15,17,19,22} assessed whether the patient had a “history of smoking” (current or former).

Outcomes were progression of COVID-19 to more severe or critical conditions or death. Six studies^{11,16,20,21,23,24} categorized the outcome as severe or critical (respiratory distress with respiratory rate ≥ 30 /min, or oxygen saturation $\leq 93\%$ at rest, or oxygenation index ≤ 300 mm Hg, based on the diagnostic and treatment guideline for SARS-CoV-2 issued by Chinese National Health Committee or the

American Thoracic Society guidelines for community acquired pneumonia^{23,24} or nonsevere, three^{10,17,18} categorized the outcome as progression or improvement, two^{8,14} categorized the outcome as intensive care unit (ICU) admission or non-ICU admission, one¹³ categorized the outcome as the primary composite endpoint (ICU admission, the use of mechanical ventilation, or death) or not, three^{9,22,26} categorized the outcome as death or survivor, one¹⁹ categorized the outcome as the occurrence of severe cases (without defining severe) or death or mild, one study¹⁵ categorized the outcome as clinical deterioration during the hospitalization and needed supplemental oxygen therapy, one¹² categorized the outcome as a need of intensive mechanical ventilators, and one²⁵ categorized the outcome as abnormal chest imaging findings.

We also conducted sensitivity analysis using the five studies^{8,9,13,16,24} that we were able to compare the association of severity of COVID-19 between current smokers and never smokers.

We computed unadjusted odds ratios (ORs) and 95% confidence interval (CI) for each study using the number of smokers (current and former) and never smokers with and without disease progression. Random effects meta-analysis was performed using the Stata version 14.0 *metan* command and using *metabias* command with Harbord and Peters to test for the presence of publication bias.

Smoking and COVID-19 Disease Progression

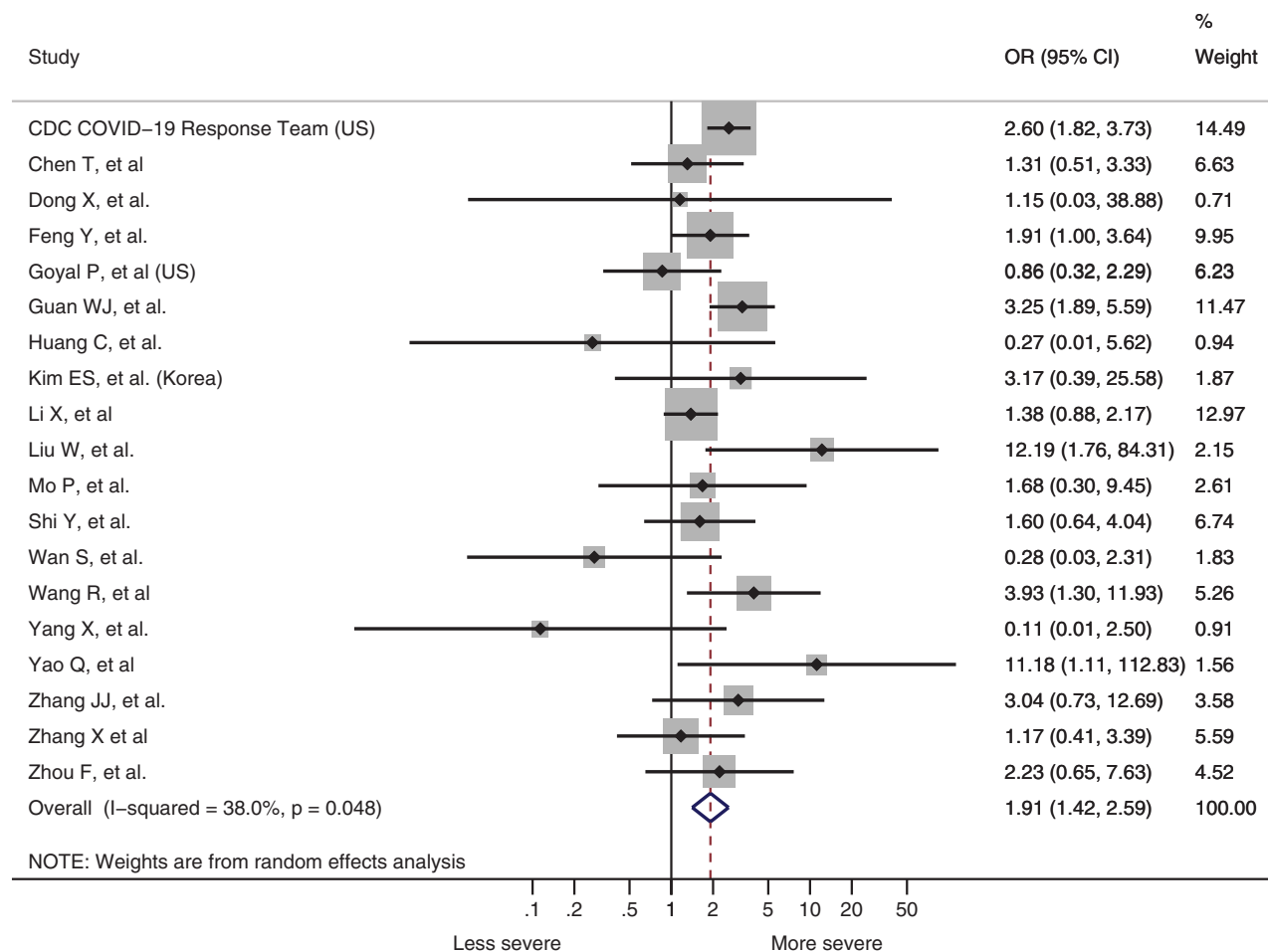


Figure 1. Smoking is associated with COVID-19 progression. All papers from China unless otherwise indicated. CI = confidence interval; OR = odds ratio.

Results

A total of 11 590 COVID-19 patients included in our meta-analysis, 2133 of whom (18.4%) experienced disease progression and 731 (6.3%) with a history of smoking. A total of 218 patients with a history of smoking (29.8%) experienced disease progression, compared with 17.6% of nonsmoking patients. The meta-analysis showed an association between smoking and COVID-19 progression (OR 1.91, 95% CI 1.42–2.59, $p = .001$) (Figure 1). There was moderate heterogeneity among the studies ($I^2 = 38\%$, $p = .048$) and no significant evidence of publication bias (Harbord's $p = .813$, Peters' $p = .941$).

Sensitivity analysis of the five studies^{8,9,13,16,24} of current smokers versus never smokers yielded a similar result (OR 1.91, 95% CI 1.10–3.29, $p = .021$). There was no evidence of significant heterogeneity ($I^2 = 53.5\%$, $p = .072$) or publication bias (Harbord's $p = .382$, Peters' $p = .512$) among the studies.

Discussion

Our analysis confirms that smoking is a risk factor for progression of COVID-19, with smokers having 1.91 times the odds of progression in COVID-19 severity than never smokers. This finding contrasts with an earlier meta-analysis,⁶ which included only five studies and used a nonstandard method to compute the meta-analysis. The finding that smoking is associated with COVID-19 progression is not surprising because of the adverse effects of smoking on pulmonary immune function.^{1,2}

Some^{27,28} have argued that the fact that reported smoking prevalence in COVID patients is lower than has been reported in the general population as evidence for a protective effect of smoking. As noted above, the low prevalence reported among COVID patients may be due to under-assessment of smoking, especially in the difficult conditions present when caring for people in overwhelmed health systems.^{29,30} In any event, our analysis shows that among those people assessed as smokers risk of disease progression is significantly increased.

Limitations

The definition of “smoking” sometimes includes former smokers and sometimes does not. Only three studies^{8,13,24} separated current and former smokers in different categories, which was not enough data to do a meta-analysis for current and former smokers separately. Because the lung recovers after someone stops smoking, including former smokers in the exposed group may bias the effect estimate to the null. Reported smoking prevalence in the 16 studies in China ranged from 3.7% to 16.8%, which was substantially lower than 27.7% (52.1% for men and 2.7% for women) smoking prevalence in 2015.³¹ Reported smoking prevalence in the United States (3.6–5.1%) and Korea (18.5%) studies were also lower than the countries' smoking prevalence; US smoking prevalence in 2018 was 13.7% (15.6% for men and 12.0% for women)³² and Korea in 2017 was 21.1% (37.0% for men and 5.2% for women).³³ It is highly likely that many smokers were misclassified as nonsmokers, which would bias the risk estimate toward the null.

This analysis is based on unadjusted ORs that were either reported in the studies¹⁷ or that we calculated based on counts in the studies.^{8–16,18–26} Only one¹⁷ of the studies reported unadjusted and adjusted ORs using multivariate analysis; after adjusting for confounding by age, maximum temperature at admission, respiratory failure, severe illness, albumin, creatinine, procalcitonin, and C-reactive protein level, the effect of smoking on disease severity increased (unadjusted: OR 12.19, 95% CI 1.76–84.31, $p = .011$; adjusted: OR 14.29, 95% CI

1.58–25.0, $p = .018$). Three peer-reviewed meta-analysis papers^{6,34,35} on association between smoking and COVID-19 were also based on unadjusted ORs, but with fewer studies included.

None of these studies assessed e-cigarette use.

All these limitations suggest that this analysis underestimates the risk of smoking in terms of increasing COVID-19 severity.

All 19 studies were of patients who had already developed COVID-19, so the risk estimate we report does not represent the effect of smoking on the risk of contracting COVID-19 in the general population. As population-level testing ramps up, it would be useful to collect data on smoking and e-cigarette use to determine what risks these behaviors impose in terms of infection.

Conclusions

Smoking is associated with COVID-19 disease progression. Physicians and public health professionals should collect data on smoking and, given the pulmonary effects of e-cigarettes,³ e-cigarette use as part of clinical assessments and add smoking (and, to be health protective, e-cigarette) cessation to the list of practices to blunt the COVID-19 pandemic.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at <https://academic.oup.com/ntr>.

Supplementary data are available at *Nicotine & Tobacco Research* online.

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Authors' Contribution

RP developed the idea for the study, collected, analyzed the data, and wrote the first draft of the manuscript. SAG assisted with revising and refining the manuscript.

Data Sharing Statement

All data used to prepare this paper are available from the cited sources.

Declaration of Interests

None declared.

References

1. Arcavi L, Benowitz NL. Cigarette smoking and infection. *Arch Intern Med*. 2004;164(20):2206–2216.
2. Bauer CMT, Morissette MC, Stämpfli MR. The influence of cigarette smoking on viral infections: translating bench science to impact COPD pathogenesis and acute exacerbations of COPD clinically. *Chest*. 2013;143(1):196–206.

3. Gotts JE, Jordt SE, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? *BMJ*. 2019;366:l5275.
4. Park JE, Jung S, Kim A, Park JE. MERS transmission and risk factors: a systematic review. *BMC Public Health*. 2018;18(1):574.
5. Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. *Tob Induc Dis*. 2020;18(March):20. doi:10.18332/tid/119324.
6. Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). *Eur J Intern Med*. 2020;75(May):107–108. doi:10.1016/j.ejim.2020.03.014
7. Berlin I, Thomas D, Le Faou AL, Cornuz J. COVID-19 and smoking [published online ahead of print April 3, 2020]. *Nicotine Tob Res*. 2020. doi:10.1093/ntr/ntaa059
8. CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019—United States, February 12–March 28, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(13):382–386.
9. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:1091.
10. Dong X, Cao YY, Lu XX, et al. Eleven faces of coronavirus disease 2019. *Allergy*. 2020;2020(00):1–11. doi:10.1111/all.14289
11. Feng Y, Ling Y, Bai T, et al. COVID-19 with different severity: a multi-center study of clinical features [published online ahead of print April 10, 2020]. *Am J Respir Crit Care Med*. 2020. doi:10.1164/rccm.202002-0445OC
12. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City [published online ahead of print April 17, 2020]. *N Engl J Med*. 2020. doi:10.1056/NEJMc2010419
13. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;2020(382):1708–1720. doi:10.1056/NEJMoa2002032
14. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
15. Kim ES, Chin BS, Kang CK, et al.; Korea National Committee for Clinical Management of COVID-19. Clinical course and outcomes of patients with severe acute respiratory syndrome coronavirus 2 infection: a preliminary report of the first 28 patients from the Korean Cohort Study on COVID-19. *J Korean Med Sci*. 2020;35(13):e142.
16. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan [published online ahead of print April 12, 2020]. *J Allergy Clin Immunol*. 2020. doi:10.1016/j.jaci.2020.04.006
17. Liu W, Tao ZW, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J (Engl)*. 2020;133(9):1032–1038.
18. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China [published online ahead of print March 16, 2020]. *Clin Infect Dis*. 2020. doi:10.1093/cid/ciaa270
19. Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. *Crit Care*. 2020;24(1):108.
20. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing [published online ahead of print March 21, 2020]. *J Med Virol*. 2020. doi:10.1002/jmv.25783
21. Wang R, Pan M, Zhang X, et al. Epidemiological and clinical features of 125 hospitalized patients with COVID-19 in Fuyang, Anhui, China [published online ahead of print April 11, 2020]. *Int J Infect Dis*. 2020. doi:10.1016/j.ijid.2020.03.070
22. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475–481. doi:10.1016/s2213-2600(20)30079-5
23. Yao Q, Wang P, Wang X, et al. Retrospective study of risk factors for severe SARS-Cov-2 infections in hospitalized adult patients [published online ahead of print April 24, 2020]. *Pol Arch Intern Med*. 2020 [published online ahead of print April 24, 2020]. doi:10.20452/pamw.15312
24. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China [published online ahead of print February 19, 2020]. *Allergy*. 2020. doi:10.1111/all.14238
25. Zhang X, Cai H, Hu J, et al. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. *Int J Infect Dis*. 2020;94(May):81–87.
26. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–1062. doi:10.1016/s0140-6736(20)30566-3
27. Fontanet A, Tondeur L, Madec Y, et al. Cluster of COVID-19 in northern France: a retrospective closed cohort study. *medRxiv*. 2020:2020. doi:10.1101/2020.04.18.20071134
28. Miyara M, Tubach F, Pourcher V, et al. Low incidence of daily active tobacco smoking in patients with symptomatic COVID-19. *Qeios*. 2020. doi:10.32388/wpp19w.3
29. Polubriaginof F, Salmasian H, Albert DA, Vawdrey DK. Challenges with collecting smoking status in electronic health records. *AMIA Annu Symp Proc*. 2017;2017:1392–1400.
30. Schofield PE, Hill DJ. How accurate is in-patient smoking status data collected by hospital admissions staff? *Aust N Z J Public Health*. 1999;23(6):654–656.
31. Parascandola M, Xiao L. Tobacco and the lung cancer epidemic in China. *Transl Lung Cancer Res*. 2019;8(Suppl 1, May):S21–S30. <http://tlcr.amegroups.com/article/view/28292>.
32. Centers for Disease Control and Prevention. *Current Cigarette Smoking Among Adults in the United States*. 2019. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm. Accessed April 6, 2020.
33. World Health Organization. *WHO Report on the Global Tobacco Epidemic, 2019: Country Profile*. Republic of Korea: World Health Organization; 2019. https://www.who.int/tobacco/surveillance/policy/country_profile/kor.pdf?ua=1. Accessed April 6, 2020.
34. Zhao Q, Meng M, Kumar R, et al. The impact of COPD and smoking history on the severity of Covid-19: a systemic review and meta-analysis [published online ahead of print April 15, 2020]. *J Med Virol*. doi:10.1002/jmv.25889
35. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis [published online ahead of print April 23, 2020]. *J Infect*. 2020. doi:10.1016/j.jinf.2020.04.021